Immunodeficiency

Abdul Ghaffar (Phone: 733-3279; ***e-mail***: ghaffar@med.sc.edu)

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TEACHING OBJECTIVES:

1. Know the primary and secondary immunodeficiencies
2. Know immunodeficiencies in AIDS and other conditions
3. Know the major primary immunodeficiencies and their features
4. Understand the relationship between site of lesion and resulting immunodeficiency
5. Know the diagnostic tests for different immunodeficiencies

READING:

Roitt, Brostoff and Male: Immunology, 6th ed. chapter 19-20.

SECONDARY AND IATROGENIC IMMUNODEFICIENCIES

Immunodeficiencies associated with infections:

Bacterial, viral, protozoan, helminthic and fungal infections may lead to B cell, T cell, PMN and macrophage deficiencies. Most prominent among these is acquired immunodeficiency syndrome (AIDS). Secondary immunodeficiencies are also seen in malignancies.

Immunologic abnormalities in the AIDS:

Cellular abnormalities of lymphocytes: There is a decrease in the number of helper_inducer (CD4) T cells, and consequently a reversal in $CD4^+/CD8^+$ T cell ratio. NK cell number is within normal range but their activity is reduced.

Functional abnormalities seen *in vivo*: AIDS patients have an increased susceptibility to infections with opportunistic organisms (*Pneumocystis carinii*, *Toxoplasma gondii*, *Cryptococcus neoformans*, herpes simplex, herpes zoster, cytomegalovirus, *Mycobacterium avium_intracellular*, *etc*). These patients also have increased incidence of neoplasms (Kaposi's sarcoma).

Delayed hypersensitivity response to common antigens such as tetanus, diphtheria, streptococcal antigen, tuberculin, Candida antigen, trichophyton, *etc*. is decreased in AIDS patients. They also fail to produce antibody in response to various antigenic challenges, both primary (*e.g.*, KLH) and recall antigens (DTP).

Immunodeficiencies associated with aging: These include a progressive decrease in thymic cortex, hypo-cellularity of and reduction in the size of thymus, a decrease in suppressor cell function and hence an increase in auto-reactivity, a decrease in CD4 cells functions. By contrast B cells functions may be somewhat elevated.

Immunodeficiencies associated with malignancies and other diseases:

B cell deficiencies have been noted in multiple myeloma, Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia and well-differentiated lymphomas. Hodgkin's disease and advanced solid tumors are associated also with impaired T_cell functions. Most chemotherapeutic agents used for treatment of malignancies are also immunosuppressive.

Other conditions in which secondary immunodeficiencies occur are sickle cell anemia, diabetes mellitus, protein calorie malnutrition, burns, alcoholic cirrhosis, rheumatoid arthritis, renal malfunction, *etc*.

PRIMARY IMMUNODEFICIENCIES

<u>Primary immunodeficiencies are inherited defects of the immune system</u>. These defects may be in the specific or nonspecific immune mechanisms. They are classified on the basis of the site of lesion in the developmental or differentiation pathway of the immune system (Figure 1. 1: reticular dysgenesis, 2: cyclic neutropenia, 3: chronic granulomatous disease, 4: severe combined immunodeficiency, 5: DiGeorge syndrome, 6: abnormal T cell functions, 7: x-linked infantile (Bruton's) hypogammaglobulinemia, 8: selective immunoglobulin deficiencies, 9: Hyper-IgM immunodeficiency).

Individuals with immunodeficiencies are susceptible to a variety of infections and the type of infection depends on the nature of immunodeficiency (Table 1).

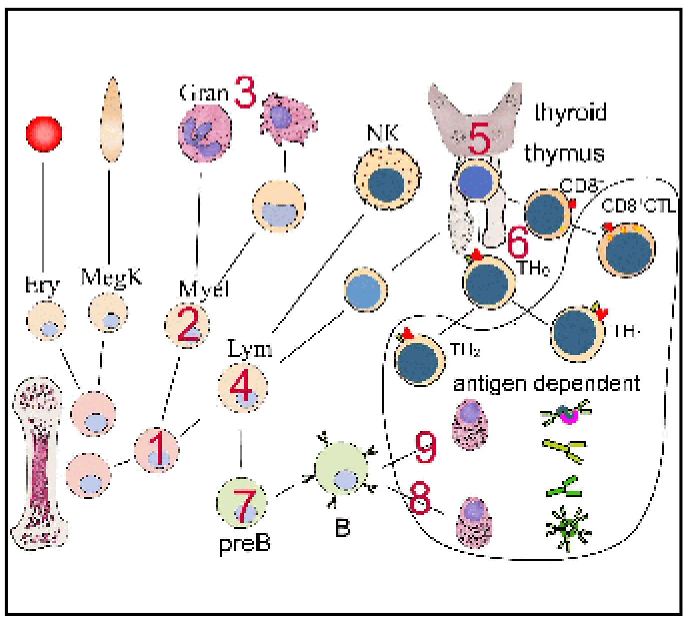


Figure 1. Developmental defects in the hemopoietic system causing different primary immunodeficiencies

Table 1. Characteristic infections in primary immunodeficiencies.

component	primary pathogen	primary site	clinical example
T-cells	intracellular, bacteria viruses, protozoa, fungi,	Many	SCID, DiGeorge
B-cells	*Haemophilus, Pneumococcus, Streptococcus*	lung, skin, CNS	Bruton's hypogammaglobulinemia IgG, IgM deficiency
	enteric bacteria and viruses and protozoa	GI, nasal and other mucosal tissues, eye	IgA deficiency
phagocytes	Staphylococcal, *Klebsiella* Pseudomonas,	lung, skin, regional lymph node	chronic granulomatous disease (CGD)
complement	*Neisseria, Haemophilus Pneumococcus Streptococcus*	CNS lung skin	C3, factors I and H, late C components

Specific immune system:

There are a variety of immunodeficiencies that result from defects in stem the cell differentiation and may involve T-cells, B-cells, and/or immunoglobulins of different classes and subclasses (Table 2).

Disorders of pleuripotential (myeloid/lymphoid) stem cells:

Reticular dysgenesis is an extremely rare but fatal abnormality. It is characterized by the absence or severe deficiency of lymphocytes and granulocytes: erythrocytes and platelets are normal.

Disorders of lymphoid stem cells:

Severe combined Immunodeficiency: Two major forms of severe combined immunodeficiencies (SCID) have been described. In about 50% of SCID patients the immunodeficiency is x_linked and it is also referred to x-linked lymphopenic hypogammaglobulinemia (sometimes called agamma-globulinemia). This form of SCID is due to a defect in **γ-chain of IL-2** receptor (CD132), also shared by IL-4, -7, -11 and 15. Consequently all these cytokine receptors that are involved in lymphocyte proliferation and/or differentiation are dysfunctional.

The other 50% of SCID are of autosomal nature and are due to a variety of defects. The most prominent among these are defects in adenosine deaminase **(ADA)** or purine nucleoside phosphorylase **(PNP)** genes **RAG1, RAG2** genes, and the **IL2 receptorș α-chain (CD25)** gene which is shared by IL7 and IL13 receptors.

Table 2. Summary of T cell and B cell immunodeficiency diseases (ID).

disease	T-cells		B-cells	immunoglobulins			inheri-tance
	No.	Fx	No	IgM	IgG	IgA	
reticular dysgenesis	A	A	A	A	A	A	u
SCID (autosomal)	A/L	A/L	A/L	A/L	A/L	A/L	a
SCID (x-linked)	A/L	A/L	A/L	A/L	A/L	A/L	x
DiGeorge's syndrome	A/L	A/L	N/V	N/V	N/V	N/V	a/x
ataxia telangiectasia	L	L	L	N/V	L/V	L	a
Wiskott-Aldrich	?V	L	L/V	L	N	H	x
				(also	high	IgE)	
x-linked hypo-- globulinemia	N	N	L	L	L	L	x
selective IgA ID							
hyper-IgM hypo-- globulinemia	N	N	N	N	L/V	L	a/x
transient hypo-- globulinemia	N	N	N	H	L	L	x
common variable hypo--	N	N	N	N	L	L	a?
globulinemia (teens-adult)	N	N	N	N	L	L	none

A: absent; a: autosomal; H: high; L: low; N: normal; U; unknown; V: variable; x: x_linked

The absence of ADA and PNP results is the accumulation of dATP or dGTP, respectively, that cause toxicity to lymphoid stem cells. **RAG1, RAG2** genes are needed for the recombination of VD/VDJ genes in both B and T cells and their absence results in the absence of antigen receptor and hence lack of T and B cell differentiation. The IL2 receptor γ-chain defect results in the absence of a high affinity IL2 receptor and possibly IL7 and IL13 receptors and hence lack of T and B cell proliferation.

Both forms of SCID are characterized by an **<u>absence of T cell and B cell immunity and absence (or extremely low numbers) of circulating T and B lymphocytes</u>**. Thymic shadow is absent on X_rays. Patients with SCID are susceptible to a variety of bacterial, viral, mycotic and protozoan infections. <u>If suspected of SCID, the patient must not receive live vaccines, as it will result in progressing disease</u>.

SCID diagnosis is based on enumeration of T (CD3) and B (CD19) cells and immunoglobulin measurement. Severe combined immunodeficiency can be treated with bone marrow transplant (see MHC and transplantation. Recently, autosomal SCID patients with ADA deficiency have been treated with a retroviral vector transfected with the appropriate gene with some success.

Disorders of T cells:

DiGeorge's syndrome: This the most clearly defined T_cell immunodeficiency and is also known as congenital thymic aplasia/hypoplasia, or immunodeficiency with hypoparathyroidism. The syndrome is associated with hypoparathyroidism, congenital heart disease, low set notched ears and fish shaped mouth. These defects result from abnormal development of fetus during 6th-10th week of gestation when parathyroid, thymus, lips, ears and aortic arch are being formed. No chromosomal association is clear and not all DiGeorge syndrome babies have thymic aplasia. A thymic graft taken from an early fetus (13-14 weeks of gestation) can be used for treatment. Grafts from older fetuses are likely to cause GVH reaction. In severely immunodeficient DiGeorge patients, live vaccines are like to cause progressive infections.

T cell deficiencies with variable degrees of B cell deficiency:

Ataxia_telangiectasia: This is a deficiency of T cells associated with a lack of coordination of movement (ataxis) and dilation of small blood vessels of the facial area (telangiectasis). T_cells and their functions are reduced to various degrees. B cell numbers and IgM concentrations are normal to low. **IgG is often reduced** and **IgA is considerably reduced** (in 70% of the cases). There is a high incidence of malignancy, particularly leukemias, in these patients. The defects arise from a breakage in chromosome 14 at the site of TCR and Ig heavy chain genes.

Wiskott_Aldrich syndrome: This immunodeficiency is associated with normal T cell numbers with **reduced functions**, which get progressively worse. IgM concentrations are reduced but IgG levels are normal. Both IgA and IgE levels are elevated. Boys with this syndrome develop severe eczema, petechia (due to platelet defect and thrombocytopenia). They respond poorly to polysaccharide antigens and are prone to pyogenic infections. These patients have a defective **WASP protein** which is involved in cytoskeletal reorganization.

MHC deficiency (Bare leukocyte syndrome): A number of cases have been described in which there is a defect in the MHC class II transactivator (CIITA) protein gene, which results in a lack of class-II MHC molecule on their APC. Since the positive selection of CD4 cells in the thymus depends on the presence of this MHC molecules, these patients have fewer CD4 cells and are infection prone. There are also individuals who have a defect in their transport associated protein (TAP) gene and hence do not express the class-I MHC molecules and consequently are deficient in $CD8^+$ T cells.

Disorders of B lymphocytes:

There are a number of diseases in which T cell numbers and functions are normal: B cell numbers may be low or normal but immunoglobulin levels are low. These are briefly summarized below.

x_linked infantile hypogammaglobulinemia: x-linked hypogammaglobulinemia, also referred to as Bruton's hypoglobulinemia or agammaglobulinemia, is the most severe B cell immunodeficiency in which B cell numbers and all immunoglobulin levels are very low or undetectable. The patients have a failure of B-cell maturation associated with a defective **B cell tyrosine kinase (*btk*)** gene. Diagnosis is based on enumeration of B (CD19) cells and immunoglobulin measurement.

Transient hypogammaglobulinemia: Children, at birth, have IgG levels comparable to that of the mother. The half life of IgG being 30 days, its level gradually decline, but by three months of age normal infants begin to synthesize their own IgG. In some infants, however, IgG synthesis may not begin until they are 2-3 years old. This delay has been attributed to poor T cell help. This results in a transient deficiency of IgG that can be corrected with gamma-globulin treatment.

Common variable hypogammaglobulinemia: These individuals have acquired deficiencies of IgG and IgA in the 2nd or 3rd decade of their life and are susceptible to a variety of pyogenic bacteria and intestinal protozoa. They should be treated with specially prepared -globulin for intravenous use.

IgA deficiency: IgA deficiency is the commonest of all immunodeficiencies (1/700 of all Caucasians). About 20% of individuals with IgA deficiency also have low IgG. IgA deficient patients are very susceptible to gastrointestinal, eye and nasopharyngeal infections. Patients with IgA deficiency have a high incidence of autoimmune diseases (particularly immune complex type) and lymphoid malignancies. Anti_IgA antibodies (IgG) are detected in 30 to 40 percent of patients who should not be treated with -globulins. Laboratory diagnosis is based on IgA measurement.

Selective IgG deficiency: Deficiencies of different IgG subclasses have been found. These patients are susceptible to pyogenic infections.

Hyper_IgM immunodeficiency: Individuals with this type of immunodeficiency have low IgA and IgG concentrations with abnormally high levels of IgM. These patients cannot make a switch from IgM to other classes which is attributed to a defect in CD40L on their CD4 cells. They are very susceptible to pyogenic infection and should be treated with intravenous -globulins.

Nonspecific immune systems:

Primary immunodeficiencies of the nonspecific immune system include defects in phagocytic and NK cells and the complement system proteins.

Defects of the phagocytic system:

Defects of phagocytic cells (numbers and/or functions) can lead to increased susceptibility to a variety of pyogenic bacterial infections.

Cyclic neutropenia: It is marked by low numbers of circulating neutrophil approximately every three weeks. The neutropenia lasts about a week during which the patients are susceptible to infection. The defect appears to be due to poor regulation of neutrophil production.

Chronic granulomatous disease (CGD): CGD is characterized by marked lymphadenopathy, hepato- splenomegaly and chronic draining lymph nodes. Leukocytes have poor intracellular killing and low respiratory burst. In majority of these patients, the deficiency is due to a defect in NADPH oxidase (cytochrome b_{558} : $gp91^{phox}$, or rarely $gp22^{phox}$) or other cofactor proteins ($gp47^{phox}$, $gp67^{phox}$) that participate in phagocytic respiratory burst. These patients can be diagnosed on the basis or poor **Nitroblue tetrazolium (NBT) reduction** which is a measure of respiratory burst (they are negative in the test). Interferon-γ therapy has been successful.

Leukocyte Adhesion Deficiency: Leukocytes lack the complement receptor CR3 due to a defect in CD11 or CD18 peptides and consequently they cannot respond to C3b opsonin. Alternatively there may be a defect in integrin molecules, LFA-1 or mac-1, arising from a defective CD11a or CD11b peptide, respectively. These molecules are involved in diapedesis and hence individuals with an aberration in these chains cannot respond effectively to chemotactic signals.

Chediak_Higashi syndrome: This syndrome is marked by a reduced (slower rate) intracellular killing and chemotactic movement accompanied by an impaired hagosome-lysosome fusion and lysosomal proteinase deficiency. Respiratory burst is normal. Accompanying NK cell defect and platelet and neurological disorders have been noted.

Disorders of complement system:

Complement abnormalities also lead to increased susceptibility to infections. There are genetic deficiencies of various components of complement system, which result in increased susceptibility to infections, particularly, with *Neisseria*. The most serious among these is the C3 deficiency that may arise from low C3 synthesis or deficiency in factor I or factor H.

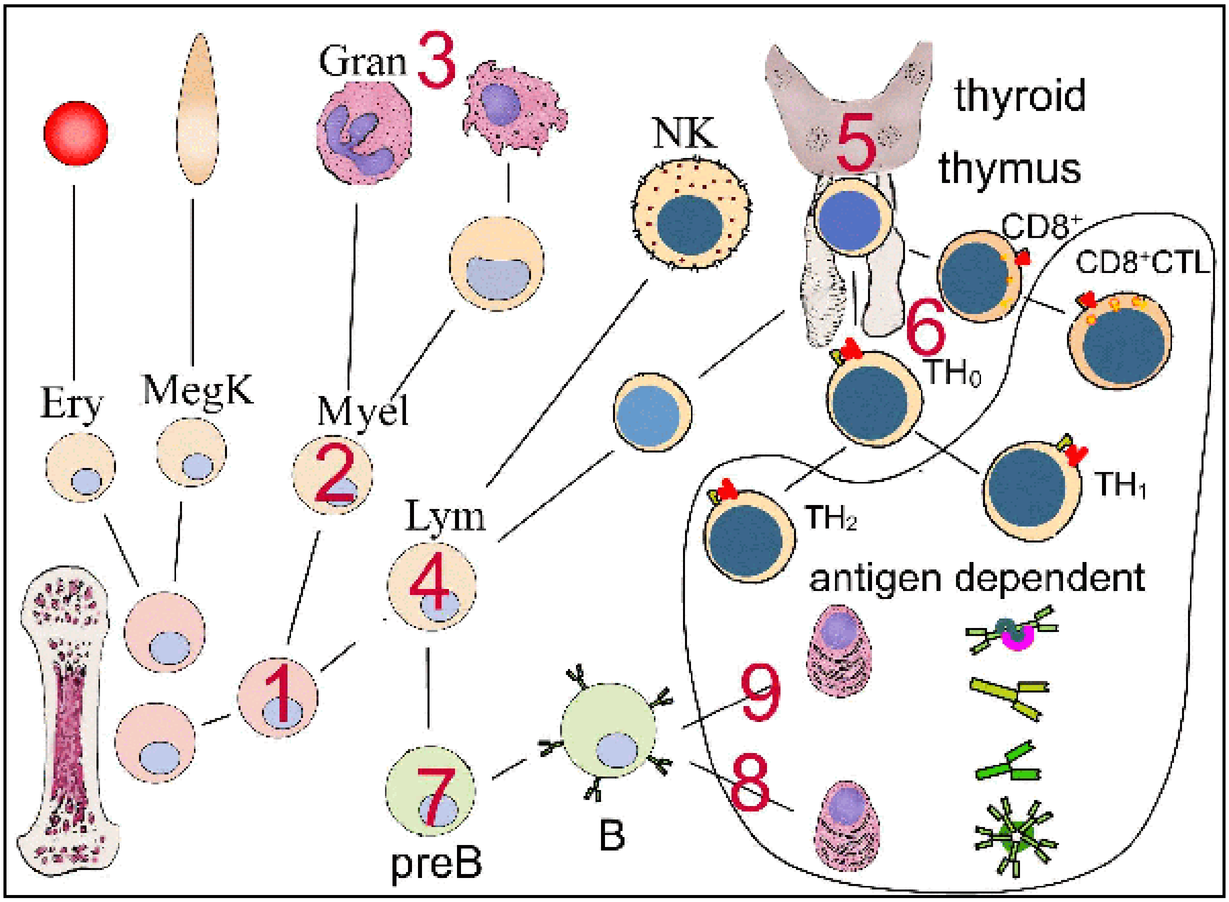


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1. Reticular dysgenesis
2. Cyclic neutropenia
3. Chronic granulomatous disease
4. Severe combined immunodeficiency
5. DiGeorge Syndrome
6. Abnormal T cell functions
7. x-linked infantile (Bruton's) hypogammaglobulinemia
8. Selective immunoglobulin deficiencies
9. Hyper IgM immunodeficiency